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Signed Andrew Gray

Dated 28 October 2004

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Request for grant of a patent

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1.	Your reference	**4-33587P1**
2.	Patent application number *(The Patent Office will fill in this part)*	0400781.1 — 14 JAN 2004
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**NOVARTIS AG** **LICHTSTRASSE 35** **4056 BASEL** **SWITZERLAND**
	Patent ADP number *(if you know it)*	712548700 5
	If the applicant is a corporate body, give the country/state of its incorporation	**SWITZERLAND**
4.	Title of invention	**Organic Compounds**
5.	Name of your agent *(If you have one)*	**Craig McLean**
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**Novartis Pharmaceuticals UK Limited** **Patents and Trademarks** **Wimblehurst Road** **Horsham, West Sussex** **RH12 5AB**
	Patents ADP number *(if you know it)*	**07181522002** ✓

6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	**Yes**

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9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	46
Claim(s)	8
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature Date

Craig McLean 13th January 2004

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr. Trevor Drew (01403) 323069

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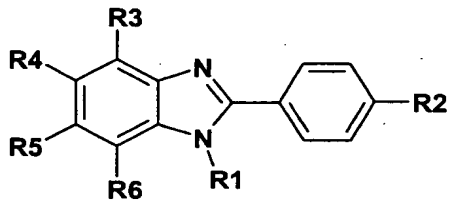
DUPLICATE

Organic Compounds

The present invention relates to bicyclic compounds, in particular to benzimidazole derivatives and to pharmaceutical uses thereof.

Accordingly the invention provides compounds of formula (I) or a pharmaceutically acceptable salt or prodrug ester thereof:



(I)

wherein

R1 is selected from the group consisting of optionally substituted (C_1-C_6 alkyl, lower alkoxy, lower alkoxy-lower alkyl, cycloalkyloxy-lower alkyl, lower thioalkyl, lower alkylthio-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, lower alkenyl and lower alkynyl);

R2 is selected from the group consisting of optionally substituted (lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, aryl, heteroaryl, aryl-lower alkyl, heteroaryl-lower alkyl);

R3 is selected from the group consisting of halo, cyano, optionally substituted (lower alkyl, lower alkoxy, lower thioalkyl, lower thioalkenyl, aryl, aryl-lower alkyl, heteroaryl, alkenyl, alkynyl, heteroaryl, aryl-lower alkyl and heteroaryl-lower alkyl and amino);

R4 is selected from the group consisting of H, halo, cyano, hydroxy, optionally substituted (lower alkyl, lower alkoxy, lower thioalkyl, lower thioalkenyl, aryl, heteroaryl, aryl-lower alkyl, heteroaryl-lower alkyl, alkenyl, alkynyl and amino);

R5 is selected from the group consisting of H, halo, cyano, hydroxyl, optionally substituted (lower alkyl, lower alkoxy, lower alkoxy-lower alkyl, aryl, heteroaryl, aryl-lower alkyl, heteroaryl-lower alkyl, alkenyl, alkynyl and amino);

R6 is selected from the group consisting of halo, cyano, optionally substituted (lower alkyl, lower alkoxy, lower thioalkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, aryl, heteroaryl, aryl-lower alkyl, heteroaryl-lower alkyl and amino).

The optional substituent or substituents on R1-R6 are independently selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl.

For the avoidance of doubt, the terms listed below are to be understood to have the following meaning throughout the present description and claims:

The term "lower", when referring to organic radicals or compounds means a compound or radical with may be branched or unbranched with up to and including 7 carbon atoms.

A lower alkyl group may be branched, unbranched or cyclic and contains 1 to 7 carbon atoms, preferably 1 to 4 carbon atoms. Lower alkyl represents, for example: methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tertiary butyl or 2,2-dimethylpropyl.

A lower alkoxy group may be branched or unbranched and contains 1 to 7 carbon atoms, preferably 1 to 6 carbon atoms. Lower alkoxy represents, for example: methoxy, ethoxy, propoxy, butoxy, isopropoxy, isobutoxy or tertiary butoxy. Lower alkoxy includes cycloalkyloxy and cycloalkyl - lower alkyloxy.

A lower alkene, alkenyl or alkenoxy group is branched or unbranched and contains 2 to 7 carbon atoms, preferably 1 to 4 carbon atoms and contains at least one carbon-carbon double bond. Lower alkene, lower alkenyl or lower alkenyloxy represents for example vinyl, prop-1-enyl, allyl, butenyl, isopropenyl or isobutenyl and the oxy equivalents thereof.

In the present application, oxygen containing substituents, e.g. alkoxy, alkenyloxy, alkynyloxy, carbonyl, etc. encompass their sulphur containing homologues, e.g. thioalkyl, alkyl-thioalkyl, thioalkenyl, alkenyl-thioalkyl, thioalkynyl, thiocarbonyl, sulphone, sulphoxide etc.

Halo or halogen represents chloro, fluoro, bromo or iodo.

Aryl represents carbocyclic aryl, heterocyclic aryl or biaryl.

Carbocyclic aryl is an aromatic cyclic hydrocarbon containing from 6 to 18 ring atoms. It can be monocyclic, bicyclic or tricyclic, for example naphthyl, phenyl, or phenyl mono-, di- or trisubstituted by one, two or three substituents.

Heterocyclic aryl is an aromatic monocyclic or bicyclic hydrocarbon containing from 5 to 18 ring atoms one or more of which are heteroatoms selected from O, N or S. Preferably there are one or two heteroatoms. Heterocyclic aryl represents, for example: pyridyl, indolyl, quinoxalinyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, benzopyranyl, benzothiopyranyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, oxadiazolyl. Heterocyclic aryl also includes such substituted radicals.

Cycloalkyl represents a cyclic hydrocarbon containing from 3 to 12 ring atoms preferably from 3 to 6 ring atoms. Cycloalkyl represents, for example: cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The cycloalkyl may optionally be substituted.

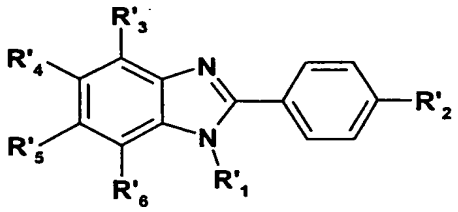
Heterocycloalkyl represents a mono-, di- or tricyclic hydrocarbon which may be saturated or unsaturated and which contains one or more, preferably one to three heteroatoms selected from O, N or S. Preferably it contains between three and 18 ring atoms. The term heterocycloalkyl is intended also to include bridged heterocycloalkyl groups such as 3-hyroxy-8-aza-bicyclo[3.2.1]oct-8-yl.

Pharmaceutically acceptable salts include acid addition salts with conventional acids, for example mineral acids, e.g. hydrochloric acid, sulfuric or phosphoric acid, or organic acids, for example aliphatic or aromatic carboxylic or sulfonic acids, e.g. acetic, trifluoroacetic,

propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, fumaric, hydroxylmaleic, pyruvic, pamoic, methanesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; also amino acids, such as arginine and lysine. For compounds of the invention having acidic groups, for example a free carboxy group, pharmaceutically acceptable salts also represent metal or ammonium salts, such as alkali metal or alkaline earth metal salts, e.g. sodium, potassium, magnesium or calcium salts, as well as ammonium salts, which are formed with ammonia or suitable organic amines.

The agents of the invention which comprise free hydroxyl groups may also exist in the form of pharmaceutically acceptable, physiologically cleavable esters, and as such are included within the scope of the invention. Such pharmaceutically acceptable esters are preferably prodrug ester derivatives, such being convertible by solvolysis or cleavage under physiological conditions to the corresponding agents of the invention which comprise free hydroxyl groups. Suitable pharmaceutically acceptable prodrug esters are those derived from a carboxylic acid, a carbonic acid monoester or a carbamic acid, advantageously esters derived from an optionally substituted lower alkanoic acid or an arylcarboxylic acid.

A second aspect of the invention provides a compound of formula (II) or a pharmaceutically acceptable salt, or prodrug ester thereof:



(II)

wherein

R'_1 is selected from the group consisting of optionally substituted (C_1-C_6 alkyl, lower alkoxy-lower alkyl, lower thioalkyl-lower alkyl, cycloalkyl-lower alkyl);

R'_2 is lower alkyl;

R'_3 is selected from the group consisting of halo, cyano, optionally substituted (lower alkyl, lower alkoxy, lower thioalkyl, lower thioalkenyl, aryl and aryl-lower alkyl);
R'_4 is selected from the group consisting of H, halo, cyano, optionally substituted (lower alkyl, aryl, aryl-lower alkyl, heteroaryl, heteroaryl-lower alkyl);

R'_5 is H, halo, or lower alkyl;

R'_6 is selected from the group consisting of halo, optionally substituted (lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl);

the optional substituent or substituents on R'_1-R'_6 being independently selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl.

With reference to formula I and II, preferably R3 is not methyl.

Preferred compounds of formula I are:

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methylsulfanyl-ethyl)-1H-benzoimidazole;

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methylsulfanyl-ethyl)-1H-benzoimidazole;

4-Bromo-1-cyclopropylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole;

4-Bromo-1-propyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole;

4-Bromo-1-butyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole;

4-Bromo-1-ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole;

{2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-benzoimidazol-1-yl]-ethyl}-dimethyl-amine;

4-Chloro-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Ethynyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-phenyl-1H-benzoimidazole;

3-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-4-yl]-phenol;

2-(4-Isopropyl-phenyl)-7-methoxy-4-[3-(2-methoxy-ethoxy)-phenyl]-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-(3,5-Dimethoxy-phenyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Methyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

5-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4,5-Dibromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Iodo-5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-trifluoromethyl-1H-benzoimidazole;

4-Bromo-5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile;

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile;

5-Benzyl-4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Bromo-5-ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile;

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-4-carbonitrile;

4-Isobutyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Benzyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4,7-Dibromo-2-(4-isopropyl-phenyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4,7-Dibromo-2-(4-isopropyl-phenyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenyl-1H-benzoimidazole;

4-Bromo-5-(3,4-dimethoxy-phenyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-phenol;

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(3-methoxy-phenyl)-1H-benzoimidazole;

3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-benzoic acid ethyl ester;

4-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-benzoic acid ethyl ester;

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-3-yl-1H-benzoimidazole;

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(3-methoxy-phenyl)-1H-benzoimidazole;

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(4-methyl-pyrazol-1-ylmethyl)-1H-benzoimidazol;

4-Bromo-5-imidazol-1-ylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

According to a third aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I) in association with a pharmaceutically acceptable excipient, diluent or carrier.

According to a fourth aspect of the invention there is provided a compound of formula (I) for promoting the release of parathyroid hormone.

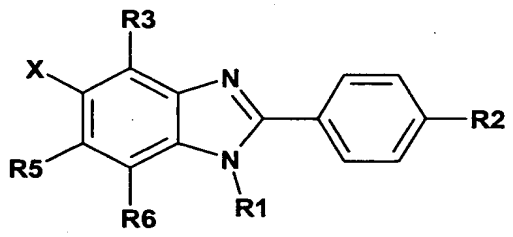
It is now well established that controlled treatment of patients with parathyroid hormone (PTH) and analogues and fragments thereof can have a pronounced anabolic effect on bone formation. Thus compounds which promote PTH release, such as the compounds of the present invention may be used for preventing or treating conditions of bone which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable.

Thus in a fifth aspect the invention includes a method for preventing or treating bone conditions which are associated with increased calcium depletion or resorption or in which

stimulation of bone formation and calcium fixation in the bone is desirable in which an effective amount of a compound of formula (I) as defined above, or a pharmaceutically-acceptable and –cleavable ester, or acid addition salt thereof is administered to a patient in need of such treatment.

In a sixth aspect the invention provides a process for preparation of a compound of formula (I) in free or salt form, comprising:

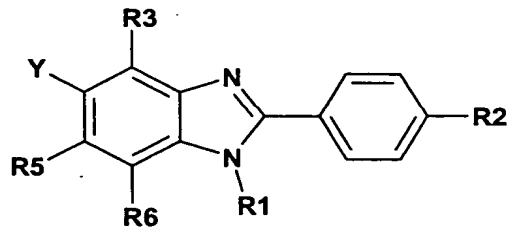
(a) introducing a group R4 into a corresponding compound of formula II, R4 being as defined above:



(II)

wherein X is any suitable group capable of substitution by R4 and wherein R1, R2, R3, R5 and R6 are as defined above; or

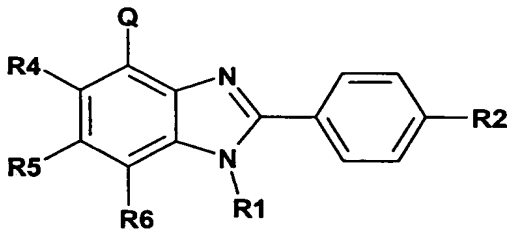
(b) for the preparation of compounds wherein R4 is an aryl-CH_2 group, appropriately introducing such aryl group by reaction with a compound of formula III:



(III)

wherein Y denotes a leaving group-CH_2- and R1, R2, R3, R5 and R6 are as defined above; or

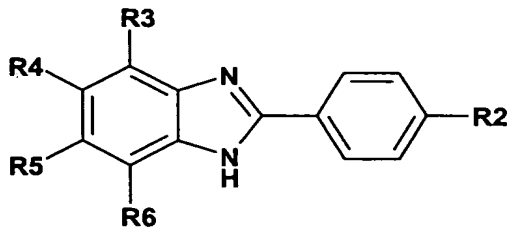
(c) introducing a group R3 into a corresponding compound of formula IV, R3 being as defined in claim 1:



(IV)

wherein Q is any suitable group capable of substitution by R3 and wherein R1, R2, R4, R5 and R6 are as defined above; or

(d) appropriately N-substituting a corresponding compound of formula V by a group R1 as defined above:



(V)

wherein R2-R6 are as defined above;

transforming the resultant compound into further compound of formula I if appropriate;

and recovering the resultant compounds of formula I in free or salt form.

The process of the invention is effected in a conventional manner. In process variant (a), X is conveniently an iodide group and the transformation is suitably performed by Suzuki coupling, for example by reacting compound II with aryl or heteroaryl-$B(OH)_2$ in the presence of a palladium catalyst. In process variant (b), Y is conveniently a methanesulfonic acid methyl ester group and compound III may be reacted with the desired aryl or heteroaryl R4 group in the presence of a base such as sodium hydride in a suitable solvent such as DMF. In process variant (c), R3 may for example represent a bromo group which may be introduced by reacting N-bromosuccinimide in a suitable solvent with a compound of formula

IV wherein Q denotes H. Process variant (d) is an N-alkylation in which R1 is conveniently an alkyl group and may be introduced by reacting a corresponding bromoalkyl with a compound of formula V in the presence of a base such as sodium hydride in suitable solvent, for example DMF.

If desired, the compound obtained may be further transformed into another compound of formula I. For example, an aryl ring substituent OH may be transformed to a 2-methoxy-ethoxy group conveniently by reaction with 2-(bromoethyl)-methyl ether in the presence of a base.

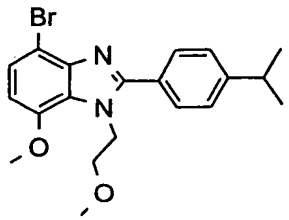
The compounds of formula I in free form may be converted into salt forms in conventional manner and vice-versa.

The compounds of the invention can be recovered from the reaction mixture and purified in conventional manner. Isomers, such as enantiomers, may be obtained in conventional manner, e.g. by fractional crystallization or asymmetric synthesis from corresponding asymmetrically substituted, e.g. optically active starting materials.

In a seventh aspect invention includes the use of a compound of formula (I) in the manufacture of a medicament for preventing or treating bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable.

Agents of the invention may be prepared by processes described below:

Example 1: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



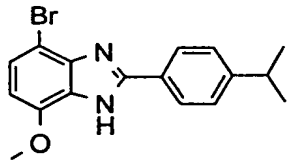
To a stirred solution of 500mg (1.45mmol) 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole in 11ml DMF, NaH (38mg, 1.6mmol) was added and stirring was continued for 1h at RT, and then the reaction mixture was heated to 60°C. 0.152ml (0.175mmol) (2-bromoethyl)-methyl ether was added and stirring was continued at this temperature for another 6h. The reaction mixture was cooled to room temperature, poured into water and extracted (3x) with ethyl acetate. The combined organic layers were washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 398mg of the title compound as colorless oil.

R_t = 2.23min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 403 $(M+1)^+$ (^{79}Br), 405 $(M+1)^+$ (^{81}Br)

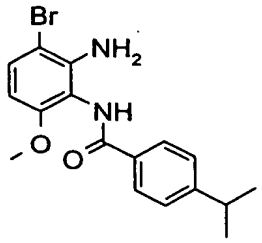
The starting materials can be prepared as follows:

a) 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole:



A solution of 1.44g (3.97mmol) N-(2-amino-3-bromo-6-methoxy-phenyl)-4-isopropyl-benzamide in 25ml glacial acetic acid was stirred at 100°C for 3h. The reaction mixture was cooled to room temperature 200ml ethyl acetate was added. The solution was washed with 4N NaOH (2x) and with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 2:1) to afford 1.12g of the title compound as slightly reddish solid.

b) N-(2-Amino-3-bromo-6-methoxy-phenyl)-4-isopropyl-benzamide:

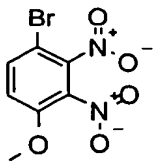


A solution of 870mg (4.01mmol) 3-bromo-6-methoxy-benzene-1,2-diamine, 1.16g (6.0mmol) EDC, 744mg (6.0mmol) DMAP and 707mg (4.01mmol) 4-isopropylbenzoic acid in 20ml dichloromethane was stirred at room temperature for 72h. The reaction mixture was concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 2:1) to afford 1.44g of the title compound as slightly reddish solid.

c) 3-bromo-6-methoxy-benzene-1,2-diamine:

A solution of 1.12g (4.04mmol) 1-bromo-4-methoxy-2,3-dinitro-benzene in 25ml THF was hydrogenated in the presence of 100mg Raney-Nickel (B113W Degussa) at normal pressure for 3h. The catalyst was filtered off and the filtrate was concentrated in vacuo to afford 871mg of the title compound as grey crystalline solid.

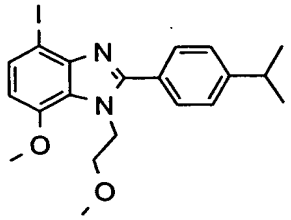
d) 1-Bromo-4-methoxy-2,3-dinitro-benzene:



1.0g (4.3mmol) 4-bromo-3-nitroanisole was nitrated by dropwise addition of 1.0ml of a mixture of 0.4 ml nitric acid (100%) and 0.6ml concentrated sulfuric acid. Stirring was continued for 1h. After that the reaction mixture was poured on water and extracted (3x) with ethyl acetate. The combined organic layers were washed with water and brine (2x), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-

chromatography on silica gel (hexane:EtOAc = 1:1) to afford 630mg of the title compound as yellow crystals.

Example 2: 4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



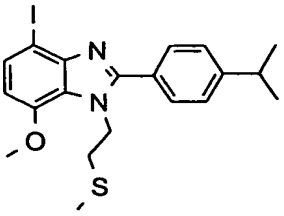
The title compound was prepared starting from 4-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole and (2-bromoethyl)-methyl ether using the same reaction conditions as described in Example1. The title compound was obtained as a colorless oil.

R_t = 2.31min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 451 $(M+1)^+$

The starting material 4-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole was prepared from 4-iodo-3-nitro-anisole using exactly the same methodology as described for in Example 1 a)-d).

Example 3: 4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methylsulfanyl-ethyl)-1H-benzoimidazole

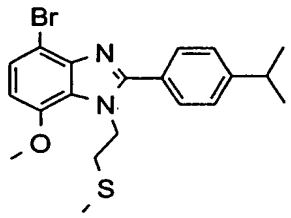


Using 1-bromo-2-methylsulfanyl-ethane instead of (2-bromoethyl)-methyl ether the title compound was prepared using the same reaction conditions as described for the preparation of Example 1.

R_t = 2.47min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 467 $(M+1)^+$

Example 4: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methylsulfanyl-ethyl)-1H-benzoimidazole

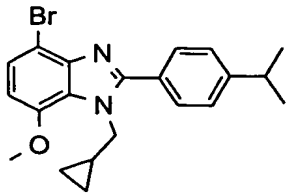


Using 1-bromo-2-methylsulfanyl-ethane instead of (2-bromoethyl)-methyl ether the title compound was prepared using the same reaction conditions as described for the preparation of Example 1.

R_t = 2.36min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 419 $(M+1)^+$ (^{79}Br), 421 $(M+1)^+$ (^{81}Br)

Example 5: 4-Bromo-1-cyclopropylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole

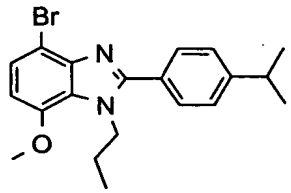


Using bromomethyl-cyclopropane instead of (2-bromoethyl)-methyl ether the title compound was prepared using the same reaction conditions as described for the preparation of Example 1.

R_t = 2.34min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 399 $(M+1)^+$ (^{79}Br), 401 $(M+1)^+$ (^{81}Br)

Example 6: 4-Bromo-1-propyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole

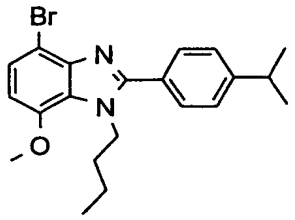


Using 1-bromo-propane instead of (2-bromoethyl)-methyl ether the title compound was prepared using the same reaction conditions as described for the preparation of Example 1.

R_t = 2.31min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 387 $(M+1)^+$ (^{79}Br), 389 $(M+1)^+$ (^{81}Br)

Example 7: 4-Bromo-1-butyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole

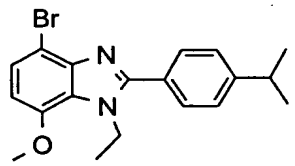


Using 1-bromo-butane instead of (2-bromoethyl)-methyl ether the title compound was prepared using the same reaction conditions as described for the preparation of Example 1.

R_t = 2.41min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 401 $(M+1)^+$ (^{79}Br), 403 $(M+1)^+$ (^{81}Br)

Example 8: 4-Bromo-1-ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole

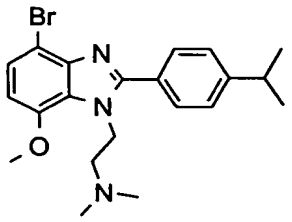


Using 1-bromo-ethane instead of (2-bromoethyl)-methyl ether the title compound was prepared using the same reaction conditions as described for the preparation of Example 1.

R_t = 2.23min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 373 $(M+1)^+$ (^{79}Br), 375 $(M+1)^+$ (^{81}Br)

Example 9: {2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-benzoimidazol-1-yl]-ethyl}-dimethyl-amine

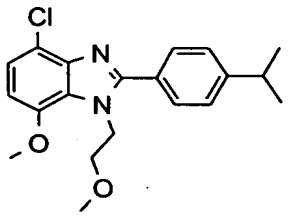


Using (2-Bromo-ethyl)-dimethyl-amine instead of (2-bromoethyl)-methyl ether the title compound was prepared using the same reaction conditions as described for the preparation of Example 1.

R_t = 1.86min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 416 $(M+1)^+$ (^{79}Br), 418 $(M+1)^+$ (^{81}Br)

Example 10: 4-Chloro-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



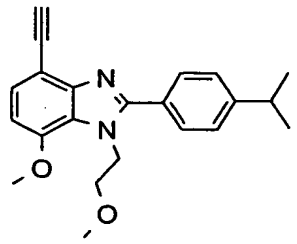
The title compound was prepared starting from 4-chloro-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole and (2-bromoethyl)-methyl ether using the same reaction conditions as described in Example1. The title compound was obtained as a colorless oil.

R_t = 2.18min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 359 $(M+1)^+$

The starting material 4-chloro-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole was prepared from 4-chloro-3-nitro-anisole using exactly the same methodology as described in Example 1 a)-d).

Example 11: 4-Ethynyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

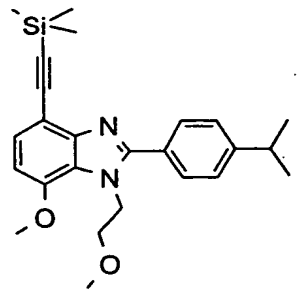


A mixture of 17mg (0.04mmol) 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trimethylsilanylethynyl-1H-benzoimidazole and 0.5ml 1N NaOH in 2ml THF/methanol (1:1) was stirred for 1hour at 60°C. The reaction mixture was cooled to room temperature and poured on water and extracted (3x) with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified on 0.5mm silica gel plates (hexane:EtOAc = 3:1) to afford 7mg of the title compound as yellow oil.

R_t = 2.11min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

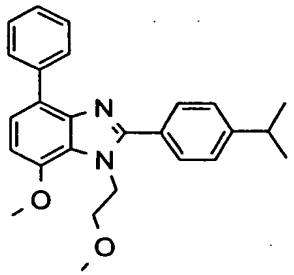
MS: 349 $(M+1)^+$

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trimethylsilanylethynyl-1H-benzoimidazole can be prepared using the following procedure:



A mixture of 50mg (0.111mmol) 4-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole, 0.1ml (0.77mmol) triethylamine, 0.1ml (0.7mmol) ethinyltrimethylsilane and 5mg palladium-II-acetate in 1ml acetonitrile was stirred at 50°C for 3hours. Then the reaction mixture was cooled to room temperature and poured on water and extracted (3x) with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 17mg of the title compound as colorless oil.

Example 12: 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-phenyl-1H-benzoimidazole

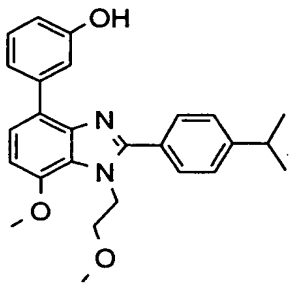


A mixture of 100mg (0.25mmol) 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole, 45mg (0.424mmol) sodium carbonate, 34mg (0.275mmol) phenyl-boronic acid and 10mg tetrakis(triphenylphosphine) palladium in 10ml toluene/water (3:1) was stirred at 100°C for nine hours. Then the reaction mixture was cooled to room temperature and poured on water and extracted (3x) with ethyl acetate. The combined organic layers were washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 4:1) to afford 53mg of the title compound as a white crystalline solid.

R_t = 2.21min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 401 $(M+1)^+$

Example 13: 3-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-4-yl]-phenol

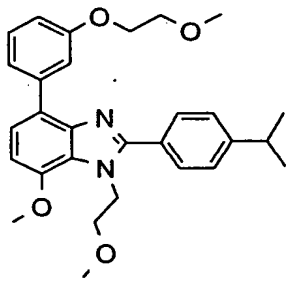


The title compound was obtained using 3-hydroxyphenyl-boronic acid instead of phenyl-boronic acid using the same procedure as described for the preparation of Example 12 as a white crystalline solid.

R_t = 2.07min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 417 $(M+1)^+$

Example 14: 2-(4-Isopropyl-phenyl)-7-methoxy-4-[3-(2-methoxy-ethoxy)-phenyl]-1-(2-methoxy-ethyl)-1H-benzoimidazole



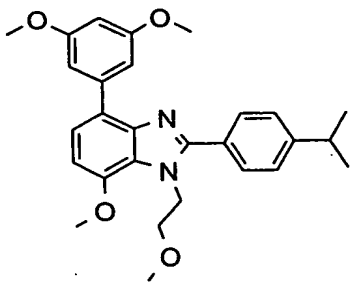
5mg (0.2mmol) NaH was added to a solution of 70mg (0.173mmol) 3-[2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-4-yl]-phenol in 2ml DMF. This mixture was stirred at room temperature for 1h. After that 28mg (0.207mmol) 2-(bromoethyl)-methyl ether was added and stirring was continued for another 3h. The reaction mixture was poured on water and extracted (3x) with ethyl acetate. The combined organic layers were

washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 70mg of the title compound as a colorless oil.

R_t = 2.18min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 475 $(M+1)^+$

Example 15: 4-(3,5-Dimethoxy-phenyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

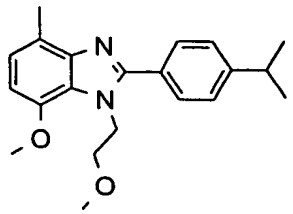


The title compound was obtained using 3,5-dimethoxyphenyl-boronic acid instead of phenyl-boronic acid using the same procedure as described for the preparation of Example 12 as a colorless oil.

R_t = 2.20min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 461 $(M+1)^+$

Example 16: 4-Methyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



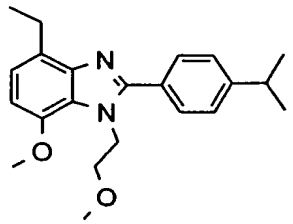
The title compound was prepared starting from 4-methyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole and (2-bromoethyl)-methyl ether using the same reaction conditions as described in Example1. The title compound was obtained as a colorless oil.

R_t = 2.01min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 339 $(M+1)^+$

The starting material 4-methyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole was prepared from 4-methyl-3-nitro-anisole using exactly the same methodology as described for in Example 1 a)-d).

Example 17: 4-Ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



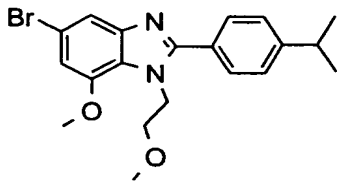
To a solution of 150mg (0.223mmol) 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole in 8ml THF, 0.289ml tert-butyllithium (1.7M in pentane) was slowly added at -78°C. This mixture was stirred for 1h at -78°C then 54µl (0.669mmol) ethyl iodide was added. The reaction mixture was warmed to room temperature and stirring was continued for 12h. The reaction mixture was cooled to room temperature, poured on water and extracted (3x) with ethyl acetate. The combined organic layers were washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was

purified by flash-chromatography on silica gel (hexane:EtOAc = 2:1) to afford 25mg of the title compound as a colorless oil.

R_t = 2.05min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 353 $(M+1)^+$

Example 18: 5-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

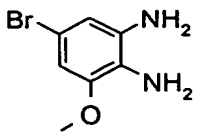


The title compound and the precursors can be prepared using the same synthesis sequence as described in example 1 from 5-Bromo-3-methoxy-benzene-1,2-diamine.

R_t = 2.13min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 403 $(M+1)^+$ (^{79}Br), 405 $(M+1)^+$ (^{81}Br)

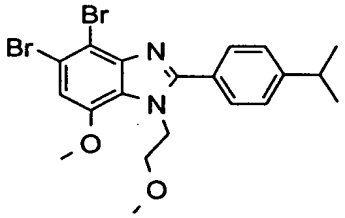
a) 5-Bromo-3-methoxy-benzene-1,2-diamine:



A solution of 2.0g (8.1mmol) 4-Bromo-2-methoxy-6-nitro-phenylamine [Zhou, Q-T., et al. *Huaxue Xuebao* **1980**, *38*(5), 507-10] in 50ml methanol/water (2:1) was hydrogenated in the presence of 200mg Pt/C (Engelhard 4709) at normal pressure for 3h. Then the catalyst was

filtered off and the filtrate was concentrated in vacuo to afford 1.5g of the title compound as an oil.

Example 19: 4,5-Dibromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

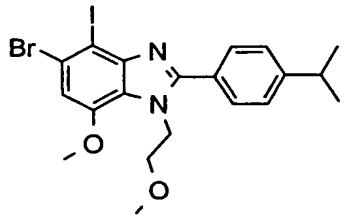


To a solution of 403mg (1.0 mmol) 5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole in 8ml glacial acetic acid, 240mg (1.5mmol) bromine was slowly added at 10°C. The reaction mixture was allowed to warm to room temperature and was stirred for 3h. 250ml EtOAc were added and this solution was washed 1n NaOH (2x), water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was recrystallized from EtOAc/hexane to afford 30mg of the title compound as colorless crystals.

R_f = 0.23 (hexane/EtOAc = 3:1)

MS: 481 $(M+1)^+$ (2x ^{79}Br), 483 $(M+1)^+$ (^{79}Br, ^{81}Br), 485 $(M+1)^+$ (2x ^{81}Br)

Example 20: 4-Iodo-5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



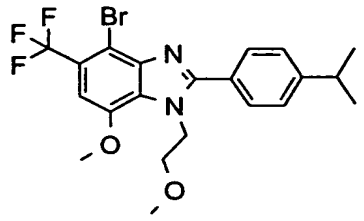
A solution of 100mg (0.248mmol) 5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole and 61mg (0.273mmol) N-iodosuccinimide in 3ml acetonitrile was refluxed for 12h. The reaction mixture was cooled to room temperature and concentrated in

vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 4:1) and recrystallisation from hexane/diethyl ether affords 82mg of the title compound as colorless crystals.

R_t = 2.60min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 529 $(M+1)^+$ (^{79}Br), 531 $(M+1)^+$ (^{81}Br)

Example 21: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-trifluoromethyl-1H-benzoimidazole



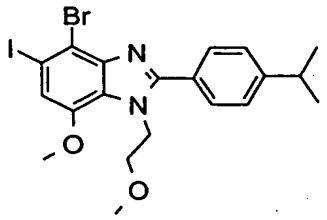
The title compound and the precursors can be prepared using the same synthesis sequence as described in example 1 and 18 from 5-trifluoromethyl-3-methoxy-benzene-1,2-diamine.

R_t = 2.73min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 471 $(M+1)^+$ (^{79}Br), 473 $(M+1)^+$ (^{81}Br)

a) 5-Trifluoro-3-methoxy-benzene-1,2-diamine can be prepared starting from 1-methoxy-3-nitro-5-trifluoromethyl-benzene using the same reaction sequence as described for the preparation of 3-bromo-6-methoxy-benzene-1,2-diamine as described in example 1.c) and d).

Example 22: 4-Bromo-5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

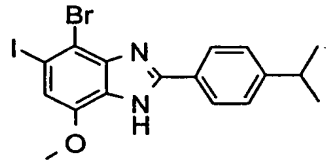


The title compound was prepared starting from 4-bromo-5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole using the same reaction conditions as described for the preparation of example 1.

R_t = 2.52min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

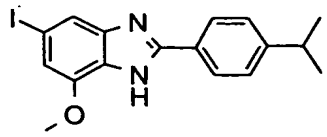
MS: 529$(M+1)^+$ (^{79}Br), 531$(M+1)^+$ (^{81}Br)

a) 4-Bromo-5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole:



To a solution of 200mg (0.51mmol) 5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole in 3ml glacial acetic acid was slowly added 82mg (0.51mmol) bromine. The reaction mixture was stirred for 45min. 30ml EtOAc were added and this solution was washed 2n NaOH, water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) and recrystallized from EtOAc/diethylether to afford 126mg of the title compound as off-white crystals.

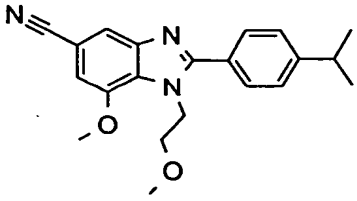
b) 5-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole was prepared starting from 4-iodo-2-methoxy-6-nitro-phenylamine using the same reaction sequence as described in examples 1 and 18.



c) 4-Iodo-2-methoxy-6-nitro-phenylamine:

A mixture of 6.2g (36.9mmol) 2-methoxy-6-nitro-phenylamine, 9.4g (37mmol) iodine and 5.8g (18.5mmol) silver sulfate in 90ml glacial acetic acid was stirred at 60°C for 12h. The reaction mixture was cooled to room temperature, poured on water and extracted (3x) with ethyl acetate. The combined organic layers were washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuum. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 2:1) to afford 8.57g of the title compound as bright red crystals.

Example 23: 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile



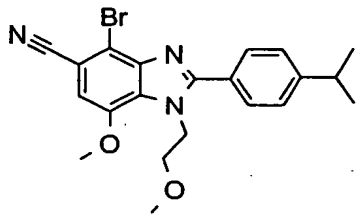
A mixture of 430mg (1.07mmol) 5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole, 125mg (1.07mmol) zinc cyanide and 20mg tetrakis(triphenylphosphine) palladium in 5ml DMF was heated in a microwave oven for 75min (180°C). After that the reaction mixture was poured on water and extracted (3x) with ethyl acetate. The combined organic layers were washed with water (3x) and brine, dried

over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 250mg of the title compound as a colorless solid.

R_t = 2.27min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 350 $(M+1)^+$

Example 24: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile

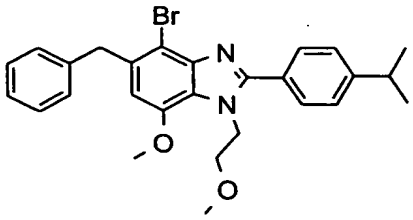


A mixture of 110mg (0.315mmol) 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile and 56mg (0.315mmol) N-bromosuccinimide in 5ml acetonitrile was stirred at reflux for 3h. Then the solvents were evaporated and the residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) and recrystallized from EtOAc/diethylether/hexane to afford 60mg of the title compound as colorless crystals.

R_t = 2.59min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 428 $(M+1)^+$ (^{79}Br), 430 $(M+1)^+$ (^{81}Br)

Example 25: 5-Benzyl-4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



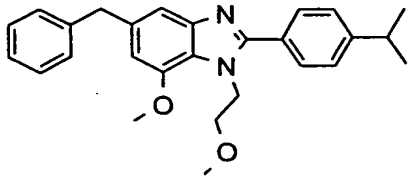
6µl (0.122mmol) bromine were added to a solution of 48mg (0.116mmol) 5-benzyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole in 6ml glacial acetic acid. The reaction mixture was stirred at room temperature for 10min. 25ml EtOAc were added and this solution was washed 4n NaOH (2x), water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was recrystallized from dichloromethane/diethyl ether/hexane to afford 40mg of the title compound as colorless crystals.

R_t = 2.38min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 493 $(M+1)^+$ (^{79}Br), 495 $(M+1)^+$ (^{81}Br)

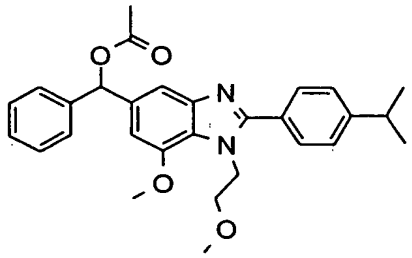
The starting materials can be prepared as follows:

a) 5-Benzyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



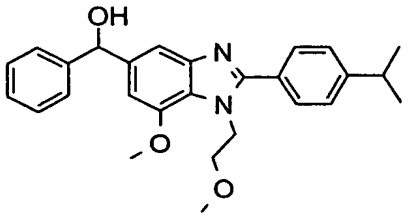
A solution of 150mg (0.317mmol) acetic acid[2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-phenyl-methyl ester in 8ml THF:MeOH = 1:2 was hydrogenated in the presence of 50mg Pd/C (Engelhard 4505). Then the catalyst was filtered off and the filtrate was concentrated in vacuo to afford 120mg of the title compound as a colorless oil.

b) Acetic acid[2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-phenyl-methyl ester



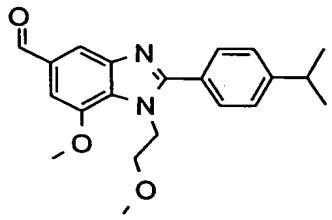
A solution of 136mg (0.30mmol) [2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-phenyl-methanol, 46µl (0.66mmol) acetyl chloride and 125µl (0.90mmol) triethylamine in 3 ml dichloromethane was stirred at room temperature for 1h. The reaction mixture was poured on water and extracted (3x) with ethyl acetate. The combined organic layers were washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 1:1) to afford 140mg of the title compound as a colorless oil.

c) [2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-phenyl-methanol



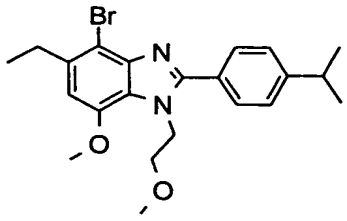
A solution of 150mg (0.426mmol) 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde in 2ml THF was treated with excess phenylmagnesiumbromide (prepared from 112µl bromobenzene and 26mg magnesium in 5ml diethyl ether). The resulting mixture was stirred at room temperature for 1h. The reaction mixture was poured on water and extracted (3x) with ethyl acetate. The combined organic layers were washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 1:2) to afford 136mg of the title compound as a white solid.

d) 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde



A mixture of 480mg (1.37mmol) 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile, 15mg Raney-Nickel (in water), 967mg (11.0mmol) sodium hypophosphite (in 10ml water), 10ml acetic acid and 20ml pyridine was stirred for 6h at 60°C. The catalyst was filtered off and the filtrate was poured on water and extracted (3x) with ethyl acetate. The combined organic layers were washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 1:1) to afford 330mg of the title compound as a white crystalline solid.

Example 26: 4-Bromo-5-ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

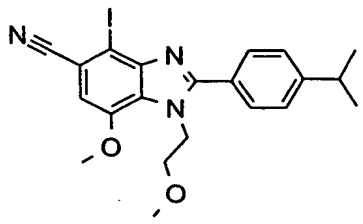


The title compound was prepared using the same methodology as described for the preparation of example 25. (Instead of phenylmagnesiumbromide, ethylmagnesiumbromide was used.)

R_t = 2.24min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 431 $(M+1)^+$ (^{79}Br), 433 $(M+1)^+$ (^{81}Br)

Example 27: 4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile

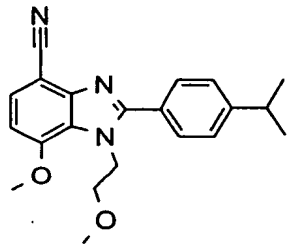


A mixture of 50mg (0.143mmol) 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile and 36mg (0.143mmol) iodine and 22mg (0.072mmol) silver sulfate in 1ml acetic acid was stirred at reflux for 3h. Then the filtrate was poured on 2n NaOH and extracted (3x) with ethyl acetate. The combined organic layers were washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 10mg of the title compound as a white crystalline solid.

R_t = 2.64min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 476 $(M+1)^+$

Example 28: 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-4-carbonitrile



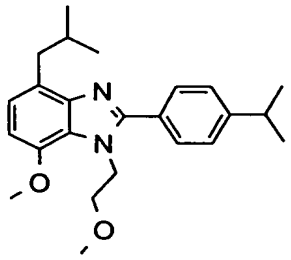
The title compound was prepared from 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole (example 1) using the same methodology as described for the preparation of example 23.

R_t = 2.42min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 350 $(M+1)^+$

Starting from 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-4-carbonitrile (example 28) the following compounds can be prepared using the same reaction sequence as described for the preparation of example 25:

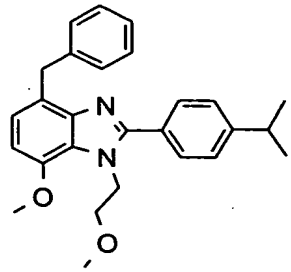
Example 29: 4-Isobutyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 2.16min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 381 $(M+1)^+$

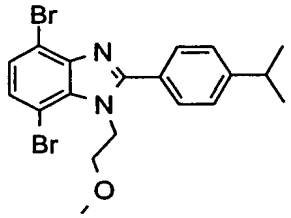
Example 30: 4-Benzyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 2.23min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 415 $(M+1)^+$

Example 31: 4,7-Dibromo-2-(4-isopropyl-phenyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole

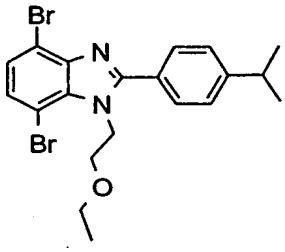


R_t = 2.73min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 451 $(M+1)^+$ (2x ^{79}Br), 453 $(M+1)^+$ (^{79}Br, ^{81}Br), 455 $(M+1)^+$ (2x ^{81}Br)

The title compound and the precursors were prepared from 3,6-Dibromo-benzene-1,2-diamine [Naef, R.; Balli, H. *Helvetica Chimica Acta* **1978**, *61*(8), 2958-73] using the same methodology as described for the preparation of example 1.

Example 32: 4,7-Dibromo-2-(4-isopropyl-phenyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole

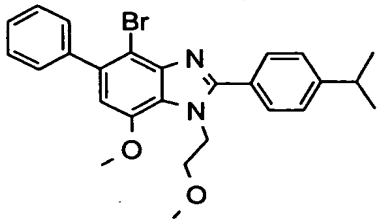


R_t = 2.82min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 465 $(M+1)^+$ (2x ^{79}Br), 467 $(M+1)^+$ (^{79}Br, ^{81}Br), 469 $(M+1)^+$ (2x ^{81}Br)

The title compound was prepared using the same methodology as described for the preparation of example 31.

Example 33: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenyl-1H-benzoimidazole



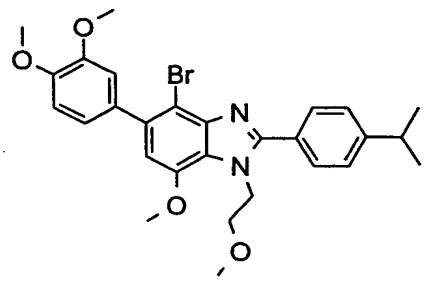
A mixture of 150mg (0.283mmol) 4-bromo-5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole (example 22), 38mg (0.312mmol) phenylboronic acid, 60mg (0.567mmol) sodium carbonate and 16mg (0.014mmol) tetrakis(triphenylphosphine)palladium in 6ml toluene/water (3:1) was stirred at 100°C for 12h. Then the reaction mixture was poured on water and extracted (3x) with ethyl acetate. The combined organic layers were washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 40mg of the title compound as a white solid.

R_t = 2.42min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 479 $(M+1)^+$ (^{79}Br), 481 $(M+1)^+$ (^{81}Br)

Using the same methodology as described in example 33 the following compounds were prepared from the corresponding boronic acids:

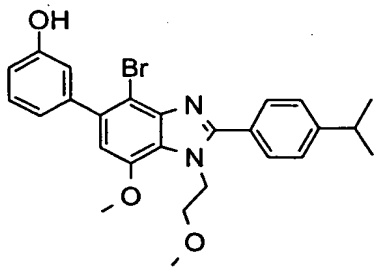
Example 34: 4-Bromo-5-(3,4-dimethoxy-phenyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 2.31min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 539 $(M+1)^+$ (^{79}Br), 541 $(M+1)^+$ (^{81}Br)

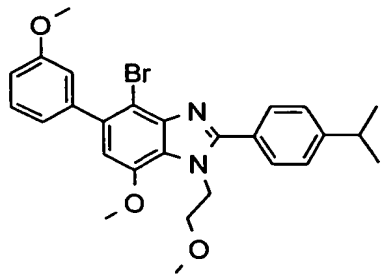
Example 35: 3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-phenol



R_t = 2.21min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 495 $(M+1)^+$ (^{79}Br), 497 $(M+1)^+$ (^{81}Br)

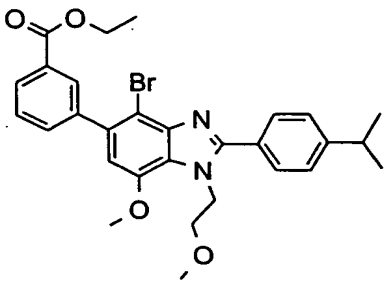
Example 36: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(3-methoxy-phenyl)-1H-benzoimidazole



R_t = 2.42min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 509 $(M+1)^+$ (^{79}Br), 511 $(M+1)^+$ (^{81}Br)

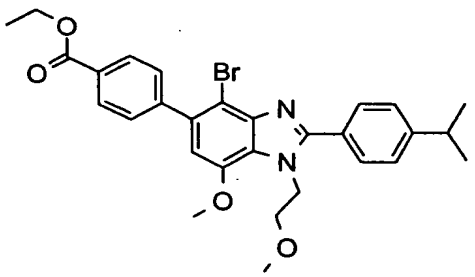
Example 37: 3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-benzoic acid ethyl ester



R_t = 2.50min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 551 $(M+1)^+$ (^{79}Br), 553 $(M+1)^+$ (^{81}Br)

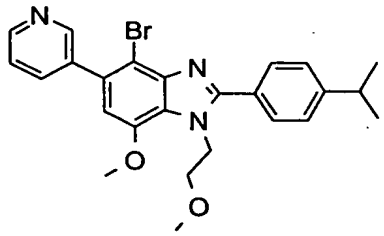
Example 38: 4-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-benzoic acid ethyl ester



R_t = 2.51min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 551 $(M+1)^+$ (^{79}Br), 553 $(M+1)^+$ (^{81}Br)

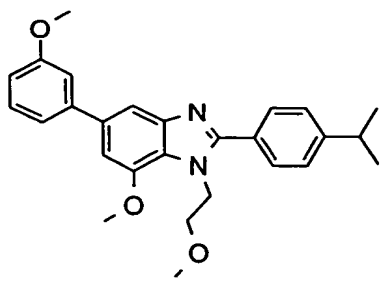
Example 39: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-3-yl-1H-benzoimidazole



R_t = 2.00min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 480 $(M+1)^+$ (^{79}Br), 482 $(M+1)^+$ (^{81}Br)

Example 40: 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(3-methoxy-phenyl)-1H-benzoimidazole

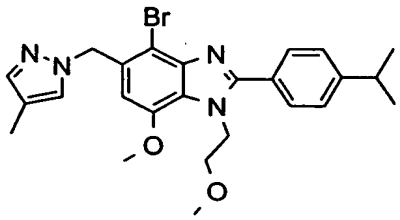


(This compound was prepared from 5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole instead of 4-bromo-5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole)

R_t = 2.06min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 417 $(M+1)^+$

Example 41: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(4-methyl-pyrazol-1-ylmethyl)-1H-benzoimidazol



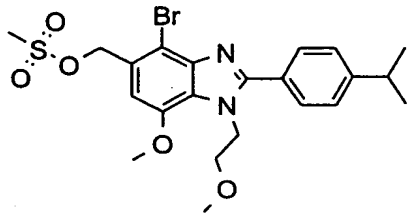
NaH (7mg, 0.3mmol) was added to a solution of 23µl (0.30mmol) 4-methylpyrazole in 2ml DMF. The resulting mixture was stirred at room temperature for 1h, then 119mg (0.23mmol) methanesulfonic acid 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl ester was added. Stirring was continued for 20h. After that the reaction mixture was poured on water and extracted (3x) with ethyl acetate. The combined organic layers were washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (dichloromethane:isopropanol = 95:5) to afford 80mg of the title compound as a white foam.

R_t = 2.28min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 497 $(M+1)^+$ (^{79}Br), 499 $(M+1)^+$ (^{81}Br)

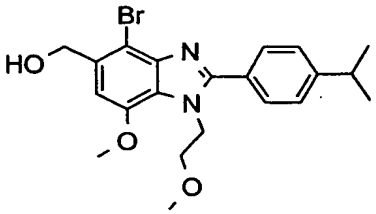
The starting materials can be prepared as follows:

a) Methanesulfonic acid 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl ester



A mixture of 100mg (0.23mmol) [4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-methanol, 26µl (0.33mmol) methanesufonyl chloride and 60µl (0.35mmol) diisopropyethylamine in 4ml dichloromethane was stirred at 0°C for 2h. The reaction mixture was poured on water and extracted (3x) with ethyl acetate. The combined organic layers were washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford 120mg of the title compound as an oil that was used directly in the next reaction.

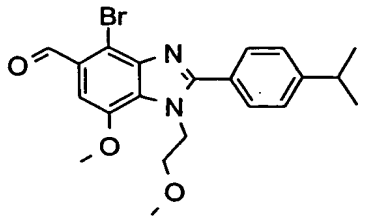
b) [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-methanol



NaBH4 (65mg, 1.72mmol) was added to a solution of 370mg (0.858mmol) 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde in 5ml absolute ethanol at 0°C. The reaction mixture was stirred at 0°C for 20min. Then the

reaction mixture was poured on water and extracted (3x) with dichloromethane/isopropanol (3:1). The combined organic layers were washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford 380mg of the title compound as a pure crystalline solid.

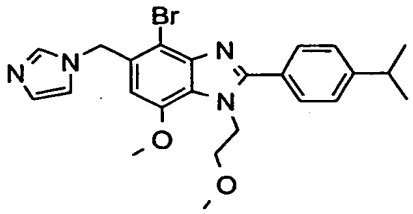
c) 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde



The title compound was prepared from 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile (example 24) using the same reaction conditions as described in example 25 d).

Reaction of methanesulfonic acid 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl ester with imidazole using the same reaction conditions as described for the preparation of example 41 led to the following compound:

Example 42: 4-Bromo-5-imidazol-1-ylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 1.93min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 483 $(M+1)^+$ (^{79}Br), 485 $(M+1)^+$ (^{81}Br)

The Agents of the Invention, as defined above, e.g., of formula (I), particularly as exemplified, in free or pharmaceutically acceptable acid addition salt form, exhibit pharmacological activity and are useful as pharmaceuticals, e.g. for therapy, in the treatment of diseases and conditions as hereinafter set forth.

Inositol phosphate formation assay:

To determine antagonistic activity at the human parathyroid calcium-sensing receptor (PcaR), compounds were tested in functional assays measuring the inhibition of calcium-induced inositol phosphate formation in CCL39 fibroblasts stably transfected with human PcaR.

Cells were seeded into 24 well plates and grown to confluence. Cultures were then labelled with [^{3}H]inositol (74 Mbq/ml) in serum-free medium for 24h. After labelling, cells were washed once with a modified Hepes-buffered salt solution (mHBS: 130 mM NaCl, 5.4 mM KCl, 0.5 mM $CaCl_2$, 0.9 mM $MgSO_4$, 10 mM glucose, 20 mM HEPES, pH 7.4) and incubated with mHBS at 37 °C in the presence of 20 mM LiCl to block inositol monophosphatase activity. Test compounds were added 3 minutes before stimulating PcaR with 5.5 mM calcium and incubations continued for further 20 min. Thereafter, cells were extracted with 10 mM ice-cold formic acid and inositol phosphates formed were determined using anion exchange chromatography and liquid scintillation counting.

Assay for intracellular free calcium:

An alternative method to determine antagonism at the PcaR consists in measuring the inhibition of intracellular calcium transients stimulated by extracellular calcium.
CCL39 fibroblasts stably transfected with human PcaR were seeded at 40'000 cells /well into 96-well Viewplates and incubated for 24 hours. Medium was then removed and replaced with fresh medium containing 2 µM Fluo-3 AM (Molecular Probes, Leiden, The Netherlands), In routine experiments, cells were incubated at 37°C, 5 % CO_2 for 1 h. Afterwards, plates were washed twice with mHBS and wells were refilled with 100 µl mHBS containing the test compounds. Incubation was continued at room temperature for 15 minutes. To record changes of intracellular free calcium, plates were transferred to fluorescence-imaging plate reader (Molecular Devices, Sunnyvale, CA, USA). A baseline consisting in 5 measurements

of 0.4 seconds each (laser excitation 488 nm) was recorded. Cells were then stimulated with calcium (2.5 mM final), and fluorescence changes recorded over a period of 3 minutes.

When measured in the above assays, Agents of the Invention typically have IC_{50}s in the range from about 1000 nM down to about 10 nM or less.

It is now well established that controlled treatment of patients with parathyroid hormone (PTH) and analogues and fragments thereof can have a pronounced anabolic effect on bone formation. Thus compounds which promote PTH release, such as the Agents of the Invention may be used for preventing or treating conditions of bone which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable.

Agents of the Invention are accordingly indicated for preventing or treating all bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable, e.g. osteoporosis of various genesis (e.g. juvenile, menopausal, post-menopausal, post-traumatic, caused by old age or by cortico-steroid therapy or inactivity), fractures, osteopathy, including acute and chronic states associated with skeletal demineralisation, osteo-malacia, periodontal bone loss or bone loss due to arthritis or osteoarthritis or for treating hypoparathyroidism.

Further diseases and disorders which might be prevented or treated include e.g. seizures, stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage such as in cardiac arrest or neonatal distress, epilepsy, neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease, dementia, muscle tension, depression, anxiety, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia, neuroleptic malignant syndrome, congestive heart failure; hypertension; gut motility disorders such as diarrhea, and spastic colon and dermatological disorders, e.g. in tissue healing, for example burns, ulcerations and wounds.

The Agents of the Invention are particularly indicated for preventing or treating osteoporosis of various genesis.

For all the above uses, an indicated daily dosage is in the range from about 0.03 to about 1000 mg, preferably 0.03 to 300, more preferably 0.03 to 30, yet more preferably 0.1 to 10 mg of a compound of the invention. Agents of the Invention may be administered twice a day or up to twice a week.

The Agents of the Invention may be administered in free form or in pharmaceutically acceptable salt form. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds. The present invention also provides a pharmaceutical composition comprising an Agent of the Invention in free base form or in pharmaceutically acceptable salt form in association with a pharmaceutically acceptable diluent or carrier. Such compositions may be formulated in conventional manner. The Agents of the Invention may be administered by any conventional route, for example parenterally e.g. in the form of injectable solutions or suspensions, enterally, e.g. orally, for example in the form of tablets or capsules or in a transdermal, nasal or a suppository form.

In accordance with the foregoing the present invention further provides:

a) an Agent of the Invention or a pharmaceutically acceptable salt thereof for use as a pharmaceutical;

b) a method for preventing or treating above mentioned disorders and diseases in a subject in need of such treatment, which method comprises administering to said subject an effective amount of an Agent of the Invention or a pharmaceutically acceptable salt thereof;

c) an Agent of the Invention or a pharmaceutically acceptable salt thereof for use in the preparation of a pharmaceutical composition e.g. for use in the method as in b) above.

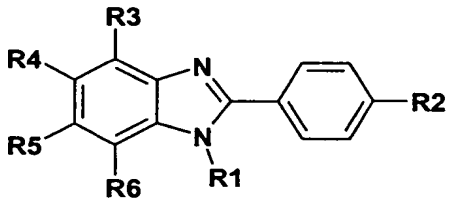
According to a further embodiment of the invention, the Agents of the Invention may be employed as adjunct or adjuvant to other therapy, e.g. a therapy using a bone resorption inhibitor, for example as in osteoporosis therapy, in particular a therapy employing calcium, a calcitonin or an analogue or derivative thereof, e.g. salmon, eel or human calcitonin, a steroid hormone, e.g. an estrogen, a partial estrogen agonist or estrogen-gestagen combination, a SERM (Selective Estrogen Receptor Modulator) e.g. raloxifene, lasofoxifene, TSE-424, FC1271, Tibolone (Livial ®), vitamin D or an analog thereof or PTH, a PTH

fragment or a PTH derivative e.g. PTH (1-84), PTH (1-34), PTH (1-36), PTH (1-38), PTH (1-31)NH_2 or PTS 893.

When the Agents of the Invention are administered in conjunction with, e.g. as an adjuvant to bone resorption inhibition therapy, dosages for the co-administered inhibitor will of course vary depending on the type of inhibitor drug employed, e.g. whether it is a steroid or a calcitonin, on the condition to be treated, whether it is a curative or preventive therapy, on the regimen and so forth.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt or prodrug ester thereof:



(I)

wherein

R1 is selected from the group consisting of optionally substituted (C_1-C_6 alkyl, lower alkoxy, lower alkoxy-lower alkyl, lower thioalkyl, lower alkylthio-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, lower alkenyl and lower alkynyl);

R2 is selected from the group consisting of optionally substituted (lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, aryl, heteroaryl, aryl-lower alkyl, heteroaryl-lower alkyl);

R3 is selected from the group consisting of halo, cyano, optionally substituted (lower alkyl, lower alkoxy, lower thioalkyl, lower thioalkenyl, aryl, aryl-lower alkyl, heteroaryl, alkenyl, alkynyl, heteroaryl, aryl-lower alkyl and heteroaryl-lower alkyl and amino);

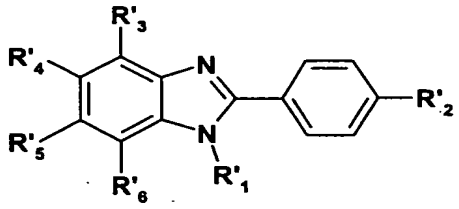
R4 is selected from the group consisting of H, halo, cyano, hydroxy, optionally substituted (lower alkyl, lower alkoxy, lower thioalkyl, lower thioalkenyl, aryl, heteroaryl, aryl-lower alkyl, heteroaryl-lower alkyl, alkenyl, alkynyl and amino);

R5 is selected from the group consisting of H, halo, cyano, hydroxyl, optionally substituted (lower alkyl, lower alkoxy, lower alkoxy-lower alkyl, aryl, heteroaryl, aryl-lower alkyl, heteroaryl-lower alkyl, alkenyl, alkynyl and amino);

R6 is selected from the group consisting of halo, cyano, optionally substituted (lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, aryl, heteroaryl, aryl-lower alkyl, heteroaryl-lower alkyl and amino);

the optional substituent or substituents on R1-R6 being independently selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl.

2. A compound of formula (II) or a pharmaceutically acceptable salt, or prodrug ester thereof:



(II)

wherein

R'_1 is selected from the group consisting of optionally substituted (C_1-C_6 alkyl, lower alkoxy-lower alkyl, lower thioalkyl-lower alkyl, cycloalkyl-lower alkyl);

R'_2 is lower alkyl;

R'_3 is selected from the group consisting of halo, cyano, optionally substituted (lower alkyl, lower alkoxy, lower thioalkyl, lower thioalkenyl, aryl and aryl-lower alkyl);

R'_4 is selected from the group consisting of H, halo, cyano, optionally substituted (lower alkyl, aryl, aryl-lower alkyl, heteroaryl, heteroaryl-lower alkyl);

R'_5 is H, halo, or lower alkyl;

R'_6 is selected from the group consisting of halo, optionally substituted (lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl);

the optional substituent or substituents on R'_1-R'_6 being independently selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl.

3. A compound according to claim 1, selected from:

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methylsulfanyl-ethyl)-1H-benzoimidazole;

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methylsulfanyl-ethyl)-1H-benzoimidazole;

4-Bromo-1-cyclopropylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole;

4-Bromo-1-propyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole;

4-Bromo-1-butyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole;

4-Bromo-1-ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole;

{2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-benzoimidazol-1-yl]-ethyl}-dimethyl-amine;

4-Chloro-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Ethynyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-phenyl-1H-benzoimidazole;

3-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-4-yl]-phenol;

2-(4-Isopropyl-phenyl)-7-methoxy-4-[3-(2-methoxy-ethoxy)-phenyl]-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-(3,5-Dimethoxy-phenyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Methyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

5-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4,5-Dibromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Iodo-5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-trifluoromethyl-1H-benzoimidazole;

4-Bromo-5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile;

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile;

5-Benzyl-4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Bromo-5-ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile;

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-4-carbonitrile;

4-Isobutyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Benzyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4,7-Dibromo-2-(4-isopropyl-phenyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4,7-Dibromo-2-(4-isopropyl-phenyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole;

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenyl-1H-benzoimidazole;

4-Bromo-5-(3,4-dimethoxy-phenyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-phenol;

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(3-methoxy-phenyl)-1H-benzoimidazole;

3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-benzoic acid ethyl ester;

4-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-benzoic acid ethyl ester;

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-3-yl-1H-benzoimidazole;

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(3-methoxy-phenyl)-1H-benzoimidazole;

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(4-methyl-pyrazol-1-ylmethyl)-1H-benzoimidazol;

4-Bromo-5-imidazol-1-ylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole;

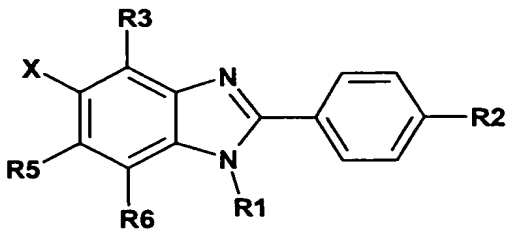
4. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 in association with a pharmaceutically acceptable excipient, diluent or carrier.

5. A compound of formula (I) as defined in claim 1 for promoting the release of parathyroid hormone.

6. A method for preventing or treating bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable in which an effective amount of a compound of formula (I) as defined in claim 1, or a pharmaceutically-acceptable and –cleavable ester, or acid addition salt thereof is administered to a patient in need of such treatment.

7. A process for the preparation of a compound of formula (I) as defined in claim 1, comprising :

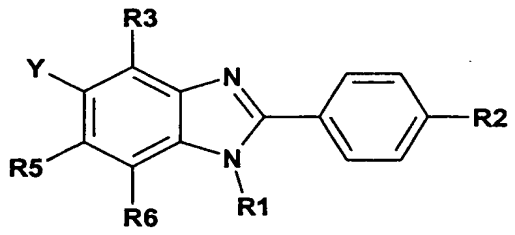
(a) introducing a group R4 into a corresponding compound of formula II, R4 being as defined in claim 1:



(II)

wherein X is any suitable group capable of substitution by R4 and wherein R1, R2, R3, R5 and R6 are as defined above; or

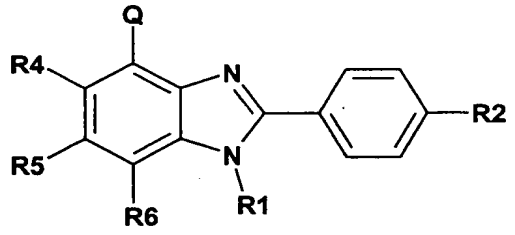
(b) for the preparation of compounds wherein R4 is an aryl-CH_2 group, appropriately introducing such aryl group by reaction with a compound of formula III:



(III)

wherein Y denotes CH_2OH or CHO; or

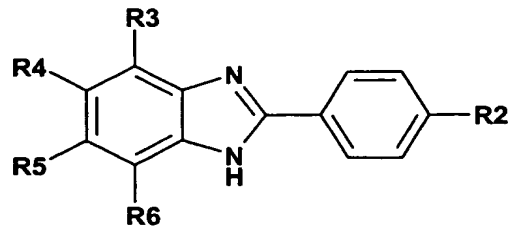
(c) introducing a group R3 into a corresponding compound of formula IV, R3 being as defined in claim 1:



(IV)

wherein Q is any suitable group capable of substitution by R3 and wherein R1, R2, R4, R5 and R6 are as defined above; or

(d) appropriately N-substituting a corresponding compound of formula V
by a group R1 as defined above:



(V)

wherein R2-R6 are as defined above;

and recovering the resultant compounds of formula I in free or salt form.

8. Use of a compound of formula (I) in the manufacture of a medicament for preventing or treating bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable.

9. All novel compounds, processes, methods and uses substantially as hereinbefore described with particular reference to the Examples.